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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/762,582	01/23/2004	Kai Licha	BOEHMER-1	3021
23599	7590	12/30/2005	EXAMINER	
MILLEN, WHITE, ZELANO & BRANIGAN, P.C. 2200 CLARENDON BLVD. SUITE 1400 ARLINGTON, VA 22201			KOSAR, ANDREW D	
			ART UNIT	PAPER NUMBER
			1654	

DATE MAILED: 12/30/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 10/762,582	Applicant(s) LICHA ET AL.	
	Examiner Andrew D. Kosar	Art Unit 1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 30 September 2005.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-34 is/are pending in the application.
- 4a) Of the above claim(s) 2,3,5,8,11,14-17 and 20-34 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1,4,6,7,9,10,12,13,18 and 19 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☒ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date <u>10/1/04</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of Group I, the species of claim 9, in the reply filed on September 30, 2005 is acknowledged. The traversal is on the ground(s) that burden has not been established by the examiner. This is not found persuasive, as the Examiner set forth a *prima facie* case of burden in the requirement (see, e.g. top of page 6, *Restriction 9/7/05*), and Applicant provides no evidence that the restriction was improper.

Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

The requirement is still deemed proper and is therefore made FINAL.

The examiner has found the elected species, the indotricarbocyanine dye of claim 9, being formula (V), free of the art. The examiner extended the search to the species embraced by formulae (II), (III), (VI), (VIII) and (IX), which are embodied in claims 6, 7, 10, 12 and 13. The species of claims 6, 7, 10, 12 and 13 have also been found to be free of the art.

The examiner extended the search to the species of claims 18 and 19, corresponding to formulae (XIV) and (XV).

Claims 2, 3, 5, 8, 11, 14-17 and 20-34 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention and/or species, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on September 30, 2005.

Claims 1, 4, 6, 7, 9, 10, 12, 13, 18 and 19 have been examined on the merits.

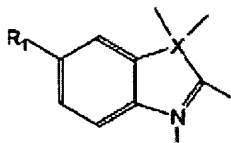
Claim Rejections - 35 USC § 112

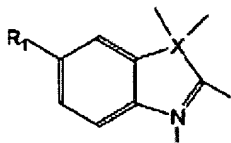
The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-24 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Please note, in the interest of compact prosecution and for Applicant's benefit, claims 2, 3, 5, 8, 11, 14-17 and 20-24 have been included in this rejection. This inclusion does not imply or suggest that the claims have been examined with regards to the prior art.

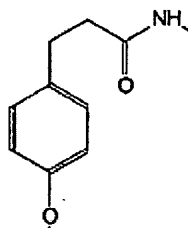
Claims 1, 2 and 6-24 recite, "Indotricarbocyanine dye ... and salts and solvates of this compound." It is unclear whether Applicant is claiming the combination of all three elements, or whether Applicant is intending to claim each individually (i.e.- "or salts or solvates"), and thus the claims are indefinite.



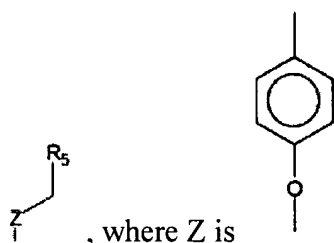
Claim 1 recites the substructure: , where X is depicted as being bonded to two methyl groups, as the image is a 'line' depiction of the compound, however X is defined as being "O, S or C that is substituted in two places" with an alkyl species. It is unclear from the structure how X is C or O or S, as the valence for any atom selected is violated. Assuming the limitation "that is substituted..." only applies to C and not O or S, carbon is hexavalent and O and S are each tetravalent. For these reasons, the claims are unclear and indefinite. It is noted that the valence of the indole nitrogen is missing the charge (+1), as identified in dependent claims.

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Claim 5 recites the limitation "R₅ is COOH or NH₂". There is insufficient antecedent basis for this limitation in the claim. Claim 1 does not allow for R₅ to be either species.

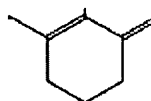


Claims 18-21 and 24 recite the substructure: , which lacks antecedent basis. The ethylene bridge, specifically, is not allowed as the substructure of formula (I):



, where Z is and R₅ is (generically) -C(O)- or -NH-, and between Z and R₅ is a methylene bridge- not an ethylene bridge. Because the species depend from claim 1, the examiner has interpreted claim 1 as allowing for the methylene bridge.

There is insufficient antecedent basis for this limitation in the claim.



Claims 18-21 and 24 recite the substructure: , and lack antecedent basis because claim 1 recites, "... in which R₆ and R₇ are CH or are connected to a hexyl ring by a C₃-alkyl...", which does not provide support for R₆ and R₇ being taken together with the sp² carbon between the R₆ and R₇ (and bonded through a C₃-alkyl) to form a hexenyl ring. Claim 1, as currently recited, indicates that the cyclohexyl group (or groups) is pendant groups from R₅ and/or R₆ or that R₅ and R₆ are connected to a shared cyclohexyl, which is not part of the backbone.

Claim Rejections - 35 USC § 103

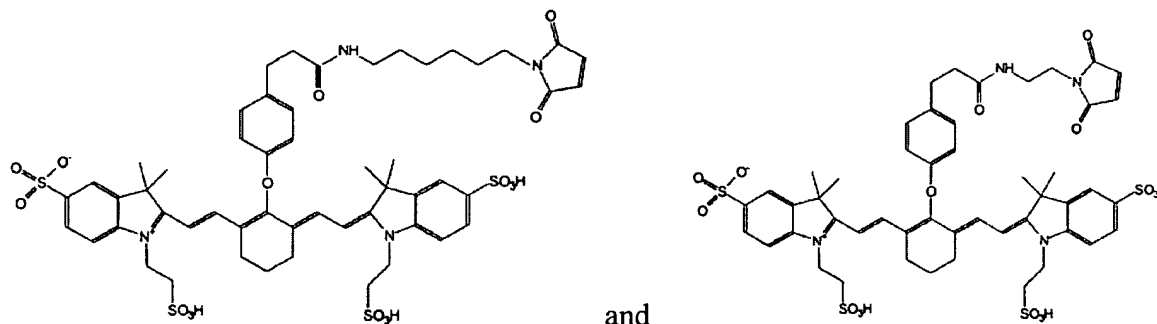
The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

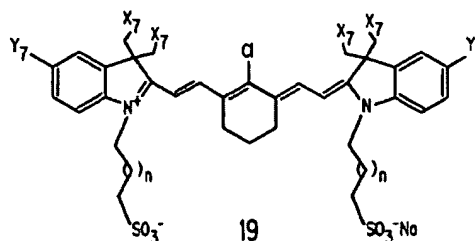
This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 4, 18 and 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over FLANAGAN (PTO-1449, 10/1/04) in view of ACHILEFU (US Patent 6,733,744 B1), ALFHEIM (US Patent 6,498,945 B1), MIWA (WO 00/16810. PTO-1449, 10/1/04), CHOREV (US Patent 5,242,680), ZAHEER (PTO-1449, 10/1/04), ROSENBLATT (M. Chorev, et al. Int. J. Peptide Protein. Res. (1992) 40, pages 445-455) and BROWN (R.D. Brown and K.S. Matthews. J. Biol. Chem. (1979) 254(12), pages 5128-5134).

The instant claims are drawn to fluorescent probes with the structures of the two species:



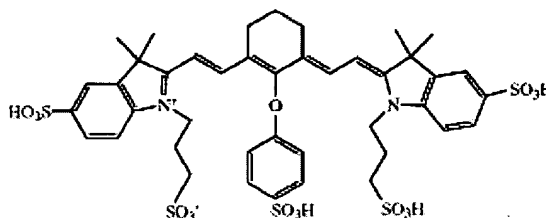
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Achilefu teaches the compound:

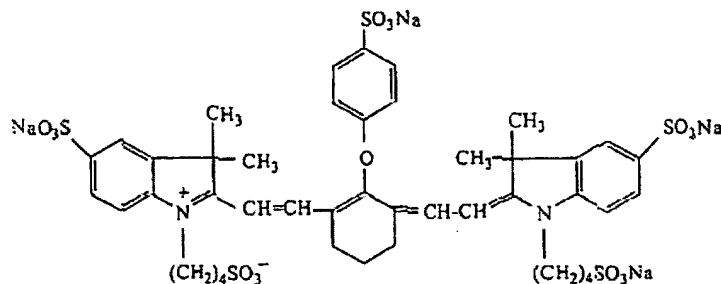
, where n is 1-3,

X_7 is H or OH and Y_7 is H, SO_3^- , COOH , CH_2COOH , or CH_2OH (Figure 5). Achilefu teaches the reaction with a R-OH moiety to form an adduct (replacement of the reactive Cl).



Alfheim teaches the compound:

(column 89).



Miwa teaches the compound:

(1st compound, top of page 102), and that “An increase in the number of sulfonic acid group[s] in a molecule or conversion to a sodium salt resulted in striking reduction of acute toxicity.” (page 84).

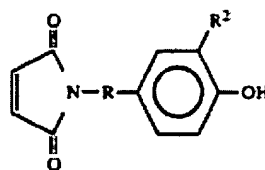
Brown is relied upon for the teachings that maleimides are selectively reactive towards sulfhydryl groups on proteins, e.g. cysteine, and are used for labeling proteins with fluorescent probes (e.g. page 5128).

Chorev teaches that, “The Bolton-Hunter reagent acylates predominantly primary ϵ -amino functions of lysine residues and to a lesser extent N-terminal α -amino functions” (column

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1, lines 59-62) and, "Furthermore, the susceptibility of the N-succinimidyl ester in the Bolton-Hunter reagent to hydrolysis limits its shelf-life and calls for introduction of large molar excess of substrate to achieve efficient incorporations" (column 2, lines 1-4) and that acylation of histidine and tyrosines may occur under 'forcing conditions' (column 2, lines 5-10).

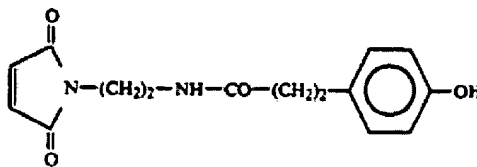
Chorev teaches that the maleimido has high specificity towards sulfhydryl and forms a stable thio-ether bond and sulfhydryl has high reactivity towards maleimido moieties (column 2, lines 12-30).



The maleimido ligand of Chorev is generically:

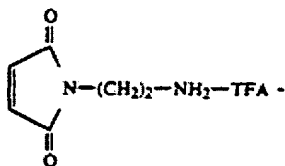
(column 2),

where R can be $(\text{CH}_2)_n\text{-NHCO-}(\text{CH}_2)_m$ and R^2 can be H, n and m are each 0-2.



Chorev further teaches the compound:

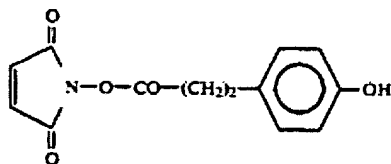
(column 3)



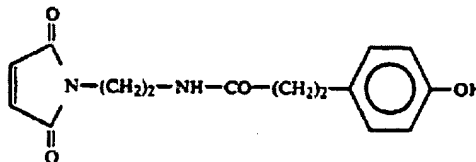
and the reaction of

VII

(column 5) with the succinimidyl ester

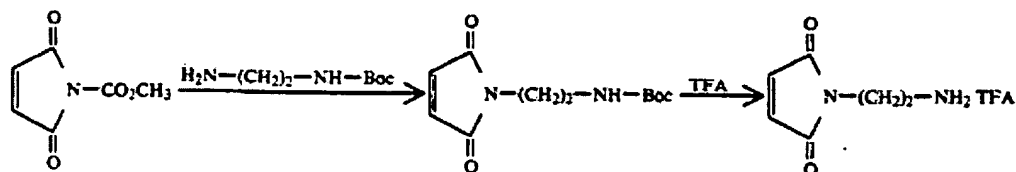


to form the compound:

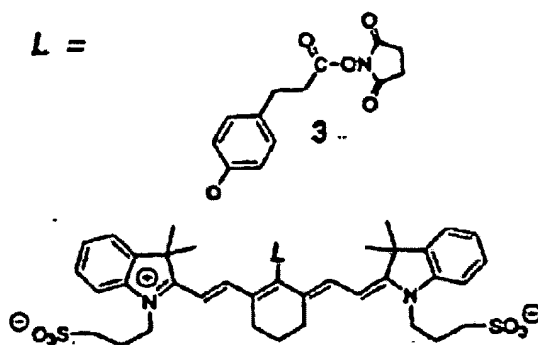


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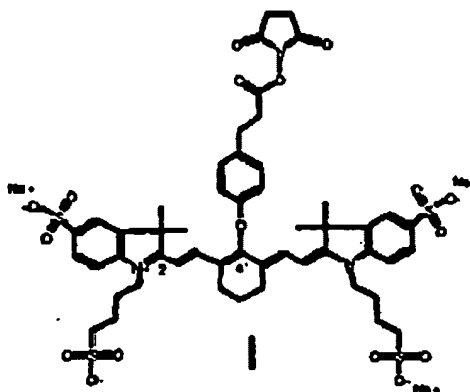
Compound (VII) is synthesized from the reaction:



Rosenblatt and Chorev both teach the reactivity of the maleimido towards sulfhydryl groups (e.g. Rosenblatt at page 446, Scheme 1; Chorev at columns 5 and 7). [It is noted that the disclosure of Chorev and the teachings of Rosenblatt are of an overlapping scope, as Chorev is the primary author of Rosenblatt].



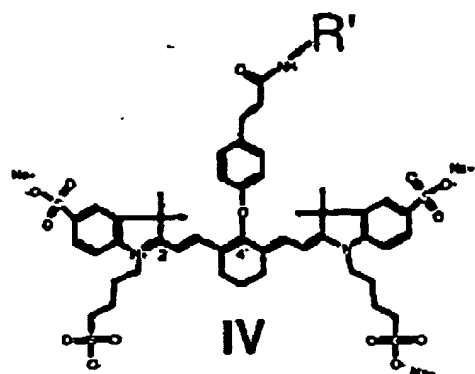
Flanagan teaches the compound: (Figure 1, page 751).



Zaheer teaches the compound: (Figure 1, page 357) and the reaction of the succinimidyl ester with a variety of compounds of the generic NH₂-

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R' (primary amine compounds) to generate compounds of the formula:



(figure 1).

The differences between that which is claimed, and that which is taught in the prior art is that while Zaheer teaches the core structure, Zaheer does not teach the R' being reacted to form the maleimide or the SO₃ groups linked to the indole nitrogen through butyl groups, and that while Flanagan teaches the core structure, Flanagan does not teach the additional SO₃ groups on the indole ring or the reaction to form the maleimide.

Alfheim teaches the core structure, but does not teach the specific linker, e.g. the maleimide linker of Chorev (or Rosenblatt). Achilefu teaches the core structure, but does not teach the phenol linker-maleimide structure.

Additionally, the difference between Chorev and that which is claimed is that Chorev teaches the phenol maleimide compound that shares a significant structural element with that of Flanagan and Zaheer and that it is used in labeling proteins, Chorev does not teach it attached to the instantly claimed fluorescent dye core structure.

It would have been obvious to one of skill in the art at the time of the invention to have made the instantly claimed compounds and the compound variants where R₅ is CONH-R₈-R₉ and R₈ is C₂-C₁₃ alkyl and R₉ is maleimide for the benefit of making a fluorescent dye that is

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selectively reactive towards sulfhydryl groups which has low toxicity and is less prone to hydrolysis.

One would have been motivated to make the fluorescent dye with the maleimide reactive group in order to make a fluorescent dye that is more stable (e.g. a longer shelf life) that is less prone to hydrolysis and is more selective towards sulfhydryl groups.

One would have a reasonable expectation for success in making the compounds, as the core structure is well known in the art, *supra*, and the reactions to form the compound are taught in the art and the compounds of the prior art. For example, one could either react the succinyl ester of Zaheer with the primary amine of Chorev (compound VII), as Chorev teaches reaction of a succinyl ester with a primary amine and Zaheer teaches reaction of the succinyl ester with a variety of primary amine compounds, including ethanolamine, or one could react the compound of Achilefu with the maleimido ligand Chorev (compound V, or the generic structure) in the reaction of Achilefu (reaction of the hydroxyl and cyclic carbon with the attached Cl (leaving group) to generate the ether linkage).

With regards to the length of the alkyl chains, the MPEP states, “A prima facie case of obviousness may be made when chemical compounds have very close structural similarities and similar utilities. “An obviousness rejection based on similarity in chemical structure and function entails the motivation of one skilled in the art to make a claimed compound, in the expectation that compounds similar in structure will have similar properties.” *In re Payne*, 606 F.2d 303, 313, 203 USPQ 245, 254 (CCPA 1979). See *In re Papesch*, 315 F.2d 381, 137 USPQ 43 (CCPA 1963) and *In re Dillon*, 919 F.2d 688, 16 USPQ2d 1897 (Fed. Cir. 1991).” See MPEP § 2144.09. In the instant case, Achilefu teaches ethyl to butyl chain lengths in the core structure, Flanagan

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teaches propyl, and Zaheer teaches butyl. One would have been motivated to make the compounds with varying alkyl chain lengths with the expectation that the compounds having close structural similarities, sharing a core structure, and all having the same function as fluorescent dyes, would have similar properties. Furthermore, the compounds taught in the art and those which are instantly claimed are closely related such that one would have been motivated to make the instantly claimed compounds with the expectation that they would have similar properties.

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Allowable Subject Matter

Claims 6, 7, 9, 10, 12 and 13 would be allowable if the rejection of the claims under 35 USC § 112, 2nd paragraph, were overcome and the claims were rewritten in independent form.

The following is a statement of reasons for the indication of allowable subject matter: The closest prior art, Zaheer, *supra*, does not teach or suggest, alone or in combination with the art of record, the compounds of claims 6, 7, 9, 10, 12 or 13, or their salts, or their solvates.

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Conclusion

Currently, **NO CLAIMS ARE ALLOWED.**

The prior art made of record on the attached PTO-892 and not relied upon in any rejection is considered pertinent to applicant's disclosure.

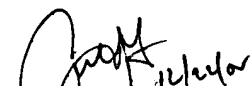
Any inquiry concerning this communication or earlier communications from the examiner should be directed to Andrew D. Kosar whose telephone number is (571)272-0913. The examiner can normally be reached on Monday - Friday 8am-430pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell can be reached on (571)272-0974. The fax phone number for the organization where this application or proceeding is assigned is (571)273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



Andrew D. Kosar, Ph.D.
Art Unit 1654



ANISH GUPTA
PRIMARY EXAMINER